Dietary and Hormonal Factors in Relation to Physical Function

DIETARY AND HORMONAL FACTORS IN RELATION TO PHYSICAL FUNCTION

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A Dissertation Submitted to the Faculty of

The Harvard T.H. Chan School of Public Health

in Partial Fulfillment of the Requirements

for the Degree of Doctor of Science

in the Department of Epidemiology

Harvard University

Boston, Massachusetts.

Date

May, 2016

Dissertation Advisor: Dr. Francine Grodstein Kaitlin A. Hagan

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ABSTRACT

Physical function is increasingly recognized as a key component of healthy aging, in particular as a core component of mobility and independent living in older adults. Prior research has also demonstrated that poor physical function is related to hospitalization, long-term nursing home care, and increased mortality among older adults. Women appear to have a greater burden of physical function impairment, although it is not certain whether this is due to gender differences in reporting of impairments, risk factor differences, or biologic differences.

In this dissertation, I examined not only risk factors for development of physical function impairment, but also explanations for apparent gender differences. First, while diet is related to numerous chronic diseases and conditions of aging, limited research has examined the role of diet, which may be an important strategy to prevent or delay decline in physical function with aging. In **Chapter 1**, I prospectively examined the association between the Alternative Healthy Eating Index-2010 (AHEI-2010), a measure of diet quality, with incident impairment in physical function among 54,762 women from the Nurses' Health Study. Overall, participants in higher quintiles of the AHEI-2010, indicating a healthier diet, were less likely to have incident physical impairment versus participants in lower quintiles over the 18 year follow-up period.

There are established sex differences in later life physical function, with a greater number of impairments in function and steeper rates of decline observed among women compared to men. It is hypothesized that some of the differences could be due to women's greater likelihood to report symptoms compared to men. Few prospective studies have investigated possible risk factor differences or differences in biological factors between men and women. In **Chapter 2**, I present the findings from an analysis investigating sex differences in relation to physical function decline. Overall, women had lower physical function scores at baseline and steeper rates of decline compared to men. These differences were partially explained by the difference in risk factors between men and women, indicating that it could be of particular importance to intervene on risk factors in women to prevent further physical function impairments with aging.

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ACKNOWLEDGMENTS

First and foremost, I thank my advisor Dr. Francine Grodstein, who provided me with an incredible amount of support and guidance throughout the doctoral program and in all other aspects of my life. I would also like to acknowledge my committee members; Drs. Jeffrey Katz, Bernard Rosner, and Meir Stampfer, whose input and advice strengthened my thesis work and allowed me to gain a deeper understanding of this research. Their insights and help are truly appreciated. I would also like to acknowledge the support I received from the Clinical Orthopedic and Musculoskeletal Education and Training Program, a National Institutes of Health funded training grant. I would like to thank the participants and staff of the Nurses' Health Study, my classmates, and the faculty and staff at the Harvard T.H. Chan School of Public Health. Finally, I thank my family, for their encouragement and support throughout my education.

INTRODUCTION

The proportion of the population 65 years and older in the United States is expected to increase to nearly 20% by the year 2030 (1). Physical function is increasingly recognized as a key component of healthy aging, in particular as a core component of mobility and independent living in older adults. Prior research has also demonstrated that poor physical function is related to hospitalization (2), long-term nursing home care (3,4), and increased mortality among older adults (4,5). Women appear to have a greater burden of physical function impairment (6), although it is not certain whether this is due to gender differences in reporting of impairments or to risk factor or biologic differences- thus it is unclear whether women may merit increased focus for preventive interventions.

In this dissertation, I examined not only risk factors for development of physical function impairment, but also explanations for apparent gender differences. First, while diet is related to numerous chronic disease and conditions of aging, surprisingly little research has examined diet and onset of physical function impairments. Studying dietary patterns is important to capture the whole diet and interactions between different dietary components; moreover diet patterns are more readily incorporated into easily understood advice for individuals (7). The Healthy Eating Index was created to evaluate diet quality, based on USDA diet guidelines. The Alternative Healthy Eating Index-2010 (AHEI-2010) was created to better focus on specific foods and nutrients predictive of chronic disease risk (8). The AHEI-2010 emphasizes the intake of whole versus refined grains and distinguishes proteins based on individual health impacts (e.g. nuts, legumes, and red and processed meats are considered separately) (8). The AHEI-2010 has been

associated with a better lipid profile, lower levels of inflammatory markers, and a lower risk of clinical vascular disease- all of which contribute to physical function (9-11).

The meager prior literature supports an association between diet quality and physical function; however, the majority of studies have been cross-sectional with modest sample sizes (12-15). In cross-sectional studies, it is plausible that better physical function may lead to better diet rather than the reverse. To our knowledge, there has been only one prospective study conducted. Among 3,000 participants in a French cohort of middle-aged adults, those with the best adherence to a pre-specified dietary guideline had an increased physical function score, as measured by the SF-36, over the 12 year follow-up period (16).

Finally, there are established sex differences in later life physical function, with a greater number of impairments in function and steeper rates of decline observed among women compared to men (6,17-19). It is hypothesized that some of the differences could be due to women's greater likelihood to report symptoms compared to men (20). There have been few prospective studies that have investigated possible risk factors differences or differences in biological factors between men and women. Thus, evaluation of risk factors profiles and plasma hormone levels in relation to physical function is a clear initial step in identifying the mechanism underlying these apparent gender disparities.

Overall, this research will provide results which will significantly enhance the current literature and permit better evaluation of diets which may be related to better physical function. This work will also allow a deeper understanding of sex differences in physical function decline and provide evidence as to whether gender differences may be due to risk factors or biological factors, as opposed to reporting differences in men and women.

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GREATER ADHERENCE TO THE ALTERNATIVE HEALTHY EATING INDEX IS ASSOCIATED WITH LOWER INCIDENCE OF PHYSICAL FUNCTION IMPAIRMENT IN THE NURSES' HEALTH STUDY

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ABSTRACT

Background: Physical function is integral to healthy aging, in particular as a core component of mobility and independent living in older adults, and is a strong predictor of mortality. Limited research has examined the role of diet, which may be an important strategy to prevent or delay decline in physical function with aging.

Methods: We prospectively examined the association between the Alternative Healthy Eating Index-2010 (AHEI-2010), a measure of diet quality, with incident impairment in physical function, measured by the Medical Outcomes Short Form-36 (SF-36) physical function scale, administered every 4 years from 1992-2008, among 54,762 women from the Nurses' Health Study. Cumulative average diet was assessed using food frequency questionnaires, administered approximately every 4 years. We used multivariable cox proportional hazards models to estimate the hazard ratios of incident impairment of physical function.

Results: Participants in higher quintiles of the AHEI-2010, indicating a healthier diet, were less likely to have incident physical impairment versus participants in lower quintiles (*P*-trend<0.001). The multivariable-adjusted hazard ratio of physical impairment for those in the top versus bottom quintile of AHEI-2010 was 0.87 (95% CI: 0.84, 0.90). For individual AHEI-2010 components, higher intake of vegetables (*P*-trend=0.003) and fruits (*P*-trend=0.02), and lower intake of sugar-sweetened beverages (*P*-trend<0.001), *trans* fat (*P*-trend=0.03), sodium (*P*-trend<0.001), and moderate alcohol (*P*-trend <0.001) were each significantly associated with reduced rates of incident physical impairment. Among top contributors to the food components of the AHEI-2010, the strongest relations were found for increased intake of oranges, orange juice, apple/pears, romaine lettuce, and walnuts. However, associations with each component and

with specific foods were generally weaker than the overall score, indicating that overall diet pattern appears more important than individual parts.

Conclusions: In this large cohort of older women, a healthier diet was associated with a lower risk of developing impairments in physical function.

INTRODUCTION

In the U.S., the proportion of the population 65 years or older is expected to reach nearly 20% by the year 2030 (1). Physical function is increasingly recognized as key to healthy aging, in particular as a core component of mobility and independent living in older adults. Prior research has demonstrated that poor physical function is related to hospitalization (2), long-term nursing home care (3,4), and increased mortality (4,5) among older adults. It is thus critical to identify modifiable factors which might prevent or delay physical function decline.

The Alternative Healthy Eating Index 2010 (AHEI-2010) was created as an update to the Alternative Healthy Eating Index and incorporates foods and nutrients predictive of chronic disease risk (6). The AHEI-2010 emphasizes the intake of whole versus refined grains and distinguishes proteins based on individual health impacts (e.g., nuts, legumes, fish, and red and processed meats are considered separately) (6). Higher adherence to the AHEI-2010 has been associated with better lipid and inflammatory profile, and decreased risk of clinical vascular disease (6). These factors have all been previously related to physical function (7-9). Prior studies have also indicated that low intake of some micronutrients may be associated with reduced physical performance, indicating that diet may play an important role in the prevention of impairment in physical function (10).

However, to our knowledge, there has been one long-term prospective study on the relationship between diet quality and physical function. Thus, we utilized data from 54,762 participants from the Nurses' Health Study to examine the association between the Alternative Healthy Eating Index-2010 and incident impairment in physical function over 18 years of follow-up.

METHODS

Study Population

The Nurses' Health Study (NHS) began in 1976, when female registered nurses, aged 30-55 years, completed a mailed questionnaire on their health and lifestyle. Follow-up questionnaires have been mailed to participants every two years thereafter and follow-up remains complete for >90%. Beginning in 1980, a food-frequency questionnaire (FFQ) was included, which was repeated in 1984, 1986 and every 4 years thereafter (11). In 1992, 1996, 2000, 2004 and 2008, the Medical Outcomes Study Short- From-36 (SF-36) was administered, a 36 item-questionnaire which evaluates eight health concepts, including physical functioning. The study was approved by the Institutional Review Board of Brigham and Women's Hospital (Boston, MA).

Diet Assessment

On the FFQ, participants report the average frequency of food consumption during the previous year, by specified units or standard portion sizes, using nine possible responses ranging from 'never or less than once per month' to 'six or more times per day'. The FFQ in the NHS has been validated carefully against repeated 7-day diet records and reproducibility of the dietary questionnaires has been documented (12, 13).

Criteria and methods for scoring of the AHEI-2010 have been previously described in detail (6); the AHEI-2010 was developed to incorporate data from food frequency questionnaires (6). Briefly, the AHEI-2010 consists of 11 components: 6 components for which higher intakes are better (vegetables, fruit, whole grains, nuts and legumes, long-chain omega-3 fatty acids, polyunsaturated fatty acids [PUFAs]); 1 component for which moderate intake is better (alcohol:

2.5 or more drinks per day is assigned 0 points, non-drinkers are assigned 2.5 points, and 0.5-1.5 drinks per day is assigned 10 points); and 4 components for which lower intake is better (sugar-sweetened beverages and fruit juice, red and processed meat, *trans* fat, and sodium). Each component is given a minimal score of 0 to indicate "worst" level of intake and a maximum score of 10 to indicate "best" level of intake, with intermediate values scored proportionally. "Best" levels of intake were determined *a priori* and based on a combination of the current dietary guidelines and the scientific literature regarding the dietary factor and chronic disease risk. All of the component scores are summed to obtain the total AHEI-2010 score, with a range from 0 (non-adherence) to 110 (perfect adherence). For these analyses, to reduce measurement error and to represent long-term dietary intake, the cumulative average of all AHEI-2010 scores from 1980 to the start of a given follow-up period was calculated at each 4-year follow-up cycle. Thus, since baseline physical function in this analysis was 1992, at the first follow-up cycle we averaged all dietary assessments from 1980 through 1990 (see Figure 1.1); at each subsequent follow-up cycle, another year of diet data were incorporated into the cumulative average.

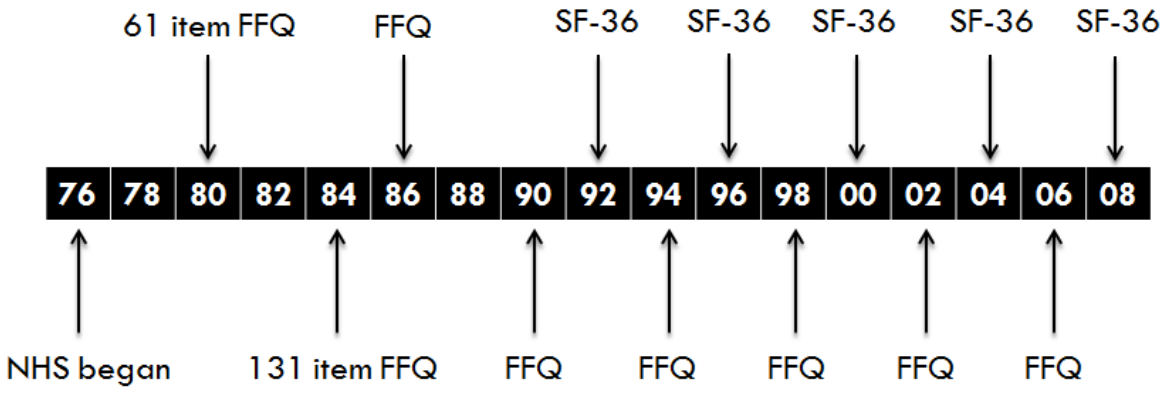

Figure 1.1. Timeline for data collection in the Nurses' Health Study.

Physical Function

Information on physical function was collected using the Medical Outcomes Short Form (SF)-36 questionnaire, a widely used and validated instrument (14). The physical function score (PFS) is a consistent and reliable predictor of morbidity and mortality in a variety of populations (5,15,16). The PFS was administered to participants starting in 1992 and every four years thereafter, and is comprised of 10 questions regarding physical limitations in performing the following activities: bathing/dressing yourself, walking one block, walking several blocks, walking more than one mile, bending/kneeling, climbing stairs, lifting groceries, moderate activities and vigorous activities. Each question has the same three response choices; each answer of 'Yes, limited a lot' is assigned one point, an answer of 'Yes, limited a little' is assigned two points, and an answer of 'No, not limited at all' is assigned three points. A raw score is calculated from the set of 10 questions and ranges from a minimum of 10 points to a maximum of 30 points. The raw score is then transformed to a 100-point scale. A PFS score of 100 is considered highest physical function and a score of 80 or less is considered significant physical impairment (17); this cutpoint has been used in other epidemiologic studies (17, 18). At the end of each follow-up cycle, incident cases of impairment were defined as a PFS decreasing to 80 or below. As an additional way to test the face validity of the PFS scoring in our cohort, we found that only 10% of participants who scored above 80 on the PFS reported adverse physical impact on their ability to perform their work or other daily activities; in contrast, 40% of even those who scored between 70 and 80 also reported limitations in daily activities due to physical health. Thus, multiple lines of evidence support this cutpoint.

Statistical Analysis

Women were excluded from this analysis if they did not complete the FFQ at analytic baseline, or had an unreasonably high (>3,500 kcal/ day) or low (<500 kcal/day) caloric intake. Additionally, women with prevalent physical impairment (physical function score [PFS] ≤80) in 1992, or women who were missing information on either the AHEI-2010 or PFS score at baseline were excluded from this analysis. The final baseline population included 54,762 women in 1992.

To evaluate the association between quintiles of the AHEI-2010 score and incident impairment in physical function, we used age adjusted and multivariable adjusted Cox proportional hazards models. Socio-demographic, lifestyle, and health-related covariates were obtained from the questionnaires and updated at each four-year time period in the analysis. Multivariable adjusted models included primary, a priori risk factors for physical function impairment: BMI (continuous), total caloric intake (quintiles), physical activity (<3.0, 3.0-8.9, 9.0-17.9, 18.0-26.9, ≥27 METs/ week), SF-36 Mental Health Index score (continuous), smoking status (never, past, current 1-14 cigarettes per day, current 15-24 cigarettes per day, ≥25 cigarettes per day), history of hypertension (yes/no), high cholesterol (yes/no), myocardial infarction (yes/no), stroke (yes/no), and type 2 diabetes (yes/no). There were few missing data, but missing data on BMI, physical activity, and smoking status were accounted for by carrying forward data from the previous questionnaire cycle or creating a missing indicator variable. In the Cox proportional hazards models examining the individual components of the AHEI-2010 score, we adjusted for the same potential confounders and also included, simultaneously in the model, the AHEI-2010 score without the component of interest. Since physical activity is so highly related to physical

function, we modeled physical activity as a continuous variable, categorical variable, and also conducted models with and without physical activity, and with and without updating physical activity at each time point.

We also conducted analyses in which we investigated the relationship between the top 5 contributors to the food component groups based on caloric intake in the study population: fruit, vegetable, nuts/legumes, red/processed meats or sugar-sweetened beverages. The specific foods were categorized into servings of 'never or <1 per month', '1-3 times per month', '1 per week', or '≥2 per week'. These are the response categories provided on the FFQ, with the top categories of intake collapsed into one category due to smaller numbers. For the nuts/legumes component (but not for primary analyses of nuts), we began follow-up in 1998 since more detailed information on specific type of nuts eaten was collected on the 1998 FFQ permitting specific analyses of different nut types. Tests for trend across quintiles of the total AHEI-2010 score and score components were calculated by treating the categories as an ordinal variable in the proportional hazards models and assigning the median value for that category.

To assess possible sources of bias, especially due to the possibility that women with early signs of physical function decline may change their diet, we conducted several secondary analyses. First, we conducted analyses in which we excluded participants with a borderline PFS (>80 to 85 points) at the start of each follow-up period. In another analysis, we imposed a 6 year lag period between diet assessment and physical function assessment. In additional research to consider diet at mid-life, we also investigated the association between diet score at baseline and subsequent physical function. Since vascular factors could be potential intermediates, we also constructed

multivariable models without these factors. To further consider vascular factors, we constructed models among those with and without hypertension at baseline and among those with and without high cholesterol at baseline. Lastly, we conducted analyses to examine effect modification by age by separately examining women less than 59, 60 to 66, and greater than 66 years at analytic baseline in 1992. All analyses were conducted in SAS version 9.3 (SAS Institute, Cary, NC, USA).

RESULTS

Characteristics of the Study Population

Characteristics of women according to quintiles of the AHEI-2010 at baseline in 1992 are presented in Table 1.1. In these descriptive results, there were few apparent differences in health and lifestyle characteristics of women across AHEI-2010 categories. However, 8.6% of women in the highest quintile (i.e. healthiest diet) of AHEI-2010 were current smokers, 16.1% had master's or doctoral degrees, and mean METs/week were 27.8; in the lowest AHEI quintile, 19.8% of women were current smokers, 6.4% had master's or doctoral degrees, and mean METs/week were 15.9.

Table 1.1. Age-standardized baseline characteristics in 1992, according to quintiles of the Alternative Healthy Eating Index-2010

	AHEI-2010				
	Quintile 1 Median=38 (n=9,748)	Quintile 2 45 (n=10,707)	Quintile 3 50 (n=10,874)	Quintile 4 56 (n=11,535)	Quintile 5 64 (n=11,898)
Mean age[1], yr	53.9 (6.9)	55.0 (7.0)	55.8 (7.0)	56.6 (6.9)	57.8 (6.8)
BMI, kg/m^2	25.3 (4.7)	25.4 (4.6)	25.3 (4.6)	25.2 (4.6)	24.7 (4.3)
Physical Activity (METs/week)	15.9 (19.2)	18.7 (22.2)	20.8 (23.7)	23.2 (24.8)	27.8 (29.4)
SF-36 Mental Health Index	76.9 (14.2)	77.7 (13.7)	78.2 (13.4)	78.5 (13.2)	79.0 (13.1)
Smoking, %					
Never	48.6	47.9	46.4	43.9	40.7
Past	31.7	36.8	39.5	44.3	50.7
Current, 1-14 cig/day	7.0	6.2	6.1	6.0	4.7
Current, 15-24 cig/day	8.6	6.6	5.7	4.4	3.1
Current, ≥25 cig/day	4.2	2.5	2.3	1.4	0.8
Alcohol intake, %					
0 g/d	52.4	41.6	35.4	30.6	24.6
1-14 g/d	34.9	48.0	54.8	60.1	67.5
≥15+ g/d	12.7	10.4	9.9	9.3	7.9
Education, %					
RN	76.2	72.3	68.8	64.2	59.0
Bachelor's	17.4	19.3	21.3	22.5	24.9
Master's/Doctoral	6.4	8.4	9.9	13.3	16.1
Hypertension, %	28.5	28.3	28.9	27.8	26.3
High Cholesterol, %	40.5	42.2	42.8	42.4	42.4
Myocardial infarction, %	0.7	0.7	0.7	0.8	0.5
Stroke, %	0.5	0.6	0.6	0.6	0.5
Type 2 Diabetes, %	3.8	3.7	3.6	3.5	3.2
Total energy intake, kcal/d	1825 (511)	1770 (515)	1742 (515)	1712 (515)	1699 (511)
Baseline PFS Score	93.9 (5.3)	94.2 (5.3)	94.5 (5.2)	94.7 (5.1)	95.0 (5.1)

Values are means(SD) or percentages

Values of polytomous variables may not sum to 100% due to rounding

[1]Value is not age adjusted

AHEI-2010 and Risk of Physical Function Impairment

In age-adjusted models (Table 1.2), the hazard ratio of incident impairment in physical function was 0.71 (95% CI: 0.69, 0.73; *P*-trend <0.001) comparing women in the highest quintile of AHEI-2010 score to the lowest quintile. After controlling for numerous potential confounders, this hazard ratio was attenuated, but remained significant (HR=0.87; 95% CI: 0.84, 0.90; *P*-trend <0.001). Results were similar after: excluding participants with a borderline PFS at the start of each cycle; imposing a 6 year lag between assessment of diet and of physical function; removing vascular factors from multivariable adjusted models; stratifying by hypertension or high cholesterol at baseline; modeling physical activity in different ways; and stratifying by age (results not shown). In analyses where we examined only baseline/mid-life AHEI-2010 (i.e., we did not update diet at each cycle), we found a similar reduced risk of impairment (e.g., for top versus bottom quintile of AHEI-2010 in 1990, HR=0.86; 95% CI: 0.83, 0.89). In addition, the correlation between diet score at baseline and diet score in 2002 was 0.52, indicating that diet patterns remained fairly consistent over time.

Table 1.2. Hazards ratios (HR) of incidence physical function impairment (measured by the Physical Function scale of the SF-36), according to quintiles of the overall AHEI-2010 score and AHEI-2010 score components

	Quintiles of AHEI Score					
	Q1	Q2	Q3	Q4	Q5	*P*-trend
Overall AHEI Score						
Median	39.9	46.8	51.9	57.3	65.2	
Person-years	41,377	45,493	47,158	50,108	53,704	
Age adjusted HR (95% CI)	1.0 (ref)	0.94 (0.91, 0.98)	0.89 (0.86, 0.92)	0.82 (0.79, 0.85)	0.71 (0.69, 0.73)	<0.001
Multivariable adjusted HR (95% CI)[1]	1.0 (ref)	0.96 (0.93, 0.99)	0.93 (0.90, 0.96)	0.90 (0.87, 0.93)	0.87 (0.84, 0.90)	<0.001
	Quintiles of natural categories of AHEI Score Components					
	Q1	Q2	Q3	Q4	Q5	*P*-trend
Vegetables						
Median, servings/day	1.63	2.42	3.09	3.90	5.34	
Person-years	42,434	46,635	48,751	49,172	50,848	
Age adjusted HR (95% CI)	1.0 (ref)	0.98 (0.95, 1.02)	0.96 (0.93, 1.00)	0.94 (0.91, 0.97)	0.87 (0.84, 0.90)	<0.001
Multivariable adjusted HR (95% CI)[2]	1.0 (ref)	0.99 (0.96, 1.03)	0.98 (0.95, 1.01)	0.98 (0.95, 1.02)	0.95 (0.91, 0.98)	0.003
Fruits						
Median, servings/day	0.54	1.01	1.43	1.92	2.81	
Person-years	44,459	47,792	48,913	48,876	47,800	
Age adjusted HR (95% CI)	1.0 (ref)	0.93 (0.90, 0.96)	0.90 (0.87, 0.93)	0.87 (0.84, 0.90)	0.79 (0.77, 0.82)	<0.001
Multivariable adjusted HR (95% CI)[2]	1.0 (ref)	0.95 (0.92, 0.98)	0.96 (0.92, 0.99)	0.95 (0.92, 0.98)	0.94 (0.91, 0.98)	0.02
Nuts and Legumes						
Median, servings/day	0.07	0.15	0.25	0.38	0.68	
Person-years	43,529	46,267	48,023	49,324	50,697	
Age adjusted HR (95% CI)	1.0 (ref)	1.04 (1.00, 1.07)	1.03 (0.99, 1.06)	1.02 (0.99, 1.05)	0.97 (0.93, 1.00)	<0.001
Multivariable adjusted HR (95% CI)[2]	1.0 (ref)	1.02 (0.98, 1.05)	1.01 (0.97, 1.04)	1.03 (0.99, 1.06)	1.06 (1.02, 1.10)	<0.001

Table 1.2 (Continued).

	Quintiles of natural categories of AHEI Score Components					
	Q1	Q2	Q3	Q4	Q5	*P*-trend
Red and Processed Meats						
Median, servings/day	0	0.45	0.77	1.10	1.61	
Person-years	46,287	48,844	49,857	48,752	44,100	
Age adjusted HR (95% CI)	1.0 (ref)	0.94 (0.91, 0.97)	1.03 (0.99, 1.06)	1.11 (1.07, 1.14)	1.20 (1.16, 1.24)	<0.001
Multivariable adjusted HR (95% CI)[2]	1.0 (ref)	0.90 (0.87, 0.93)	0.92 (0.89, 0.95)	0.94 (0.91, 0.97)	0.97 (0.94, 1.00)	0.4
Sugar-Sweetened Beverages						
Median, servings/day	0.18	0.55	0.93	1.29	2.05	
Person-years	47,908	48,423	47,191	48,126	46,192	
Age adjusted HR (95% CI)	1.0 (ref)	1.06 (1.03, 1.10)	1.03 (0.99, 1.06)	1.01 (0.98, 1.04)	1.04 (1.00, 1.07)	0.5
Multivariable adjusted HR (95% CI)[2]	1.0 (ref)	1.04 (1.00, 1.07)	1.01 (0.98, 1.05)	1.03 (0.99, 1.06)	1.08 (1.04, 1.12)	<0.001
Alcohol						
Median, drinks/day	0	0.4	0.14	0.45	1.27	
Person-years	51,988	31,210	49,156	53,398	52,088	
Age adjusted HR (95% CI)	1.0 (ref)	1.04 (1.00, 1.08)	0.93 (0.90, 0.96)	0.88 (0.85, 0.90)	0.87 (0.84, 0.90)	<0.001
Multivariable adjusted HR (95% CI)[2]	1.0 (ref)	0.94 (0.90, 0.97)	0.91 (0.88, 0.94)	0.90 (0.87, 0.93)	0.92 (0.89, 0.95)	0.02
Whole Grains						
Median, g/day	5.3	10.9	16.4	23.0	34.9	
Person-years	41,021	47,176	49,132	50,258	50,253	
Age adjusted HR (95% CI)	1.0 (ref)	1.03 (0.99, 1.06)	0.99 (0.96, 1.02)	0.96 (0.92, 0.99)	0.88 (0.85, 0.91)	<0.001
Multivariable adjusted HR (95% CI)[2]	1.0 (ref)	1.00 (0.97, 1.04)	1.00 (0.96, 1.03)	1.01 (0.97, 1.04)	1.03 (1.00, 1.07)	0.04
Trans Fats						
Median, % of energy	0.009	0.012	0.014	0.017	0.021	
Person-years	52,234	49,654	48,139	43,019	41,794	
Age adjusted HR (95% CI)	1.0 (ref)	1.14 (1.10, 1.17)	1.23 (1.19, 1.27)	1.30 (1.26, 1.34)	1.28 (1.24, 1.32)	<0.001

Table 1.2 (Continued).

	Quintiles of natural categories of AHEI Score Components					
	Q1	Q2	Q3	Q4	Q5	*P*-trend
Trans Fats (cont.)						
Multivariable adjusted HR (95% CI)[2]	1.0 (ref)	0.98 (0.95, 1.01)	1.01 (0.98, 1.04)	1.02 (0.98, 1.05)	1.02 (0.98, 1.06)	0.03
Omega-3 Fatty Acids						
Median, mg/day	75.5	130	190	270	422.5	
Person-years	44,211	45,915	49,173	49,490	49,051	
Age adjusted HR (95% CI)	1.0 (ref)	1.04 (1.01, 1.07)	101 (0.98, 1.05)	0.98 (0.95, 1.01)	0.95 (0.92, 0.98)	<0.001
Multivariable adjusted HR (95% CI)[2]	1.0 (ref)	1.01 (0.97, 1.04)	0.98 (0.95, 1.01)	0.98 (0.94, 1.01)	0.98 (0.95, 1.02)	0.2
Polyunsaturated Fatty Acids						
Median, % of energy	4.35	5.14	5.73	6.37	7.41	
Person-years	46,411	48,190	49,007	48,323	45,909	
Age adjusted HR (95% CI)	1.0 (ref)	1.06 (1.02, 1.09)	1.11 (1.08, 1.15)	1.12 (1.08, 1.16)	1.12 (1.08, 1.16)	<0.001
Multivariable adjusted HR (95% CI)[2]	1.0 (ref)	0.97 (0.94, 1.00)	0.99 (0.96, 1.03)	0.98 (0.94, 1.01)	1.01 (0.97, 1.04)	0.6
Sodium						
Median, mg/day	1357	1772	2102	2479	3113	
Person-years	47,444	49,024	48,730	48,135	44,507	
Age adjusted HR (95% CI)	1.0 (ref)	1.08 (1.04, 1.11)	1.14 (1.10, 1.18)	1.16 (1.12, 1.20)	1.26 (1.21, 1.30)	<0.001
Multivariable adjusted HR (95% CI)[2]	1.0 (ref)	1.04 (1.01, 1.08)	1.09 (1.05, 1.13)	1.10 (1.05, 1.14)	1.15 (1.10, 1.19)	<0.001

[1] Models adjusted for BMI (continuous), total caloric intake (quintiles), physical activity (<3.0, 3.0-8.9, 9.0-17.9, 18.0-26.9, ≥27 mets/wk), SF-36 mental health index (continuous), smoking (never, past, current 1-14 cigs/day, current 15-24 cigs/day, ≥25 cigs/day), hypertension (yes, no), high cholesterol (yes/no), myocardial infarction (yes/no), stroke (yes/no), type 2 diabetes (yes/no)

[2] Models adjusted for BMI (continuous), total caloric intake (quintiles), physical activity (<3.0, 3.0-8.9, 9.0-17.9, 18.0-26.9, ≥27 mets/wk), SF-36 mental health index (continuous), smoking (never, past, current 1-14 cigs/day, current 15-24 cigs/day, ≥25 cigs/day), hypertension (yes, no), high

cholesterol (yes/no), myocardial infarction (yes/no), stroke (yes/no), type 2 diabetes (yes/no) andAHEI-2010 score without the component of interest.

AHEI-2010 Score Components, Food Contributors, and Physical Function Impairment

To ascertain if specific individual components of the AHEI-2010 varied in importance, we examined the association between each AHEI-2010 component and risk of incident impairment in physical function (Table 1.2). In general, we found modest associations between each individual component and physical function, suggesting that overall dietary pattern is more important than its components. Only for sodium intake did we find hazard ratios similar in magnitude to the overall HR of AHEI-2010 score; comparing extreme quintiles of sodium as milligrams per day, the HR was 1.15 (95% CI: 1.10, 1.19; *P*-trend<0.001) .

For the five food groups in the AHEI-2010, we also considered the top individual contributors in our cohort (by caloric intake) to each food group (Table 1.3). In multivariable-adjusted models, similar to findings for AHEI-2010 components, the overall pattern appeared more important than individual foods. Among the foods examined, the strongest relations were found for greater intake of oranges, orange juice, apples and pears, romaine or leaf lettuce and walnuts; we found a HR of 0.91 (95% CI: 0.88, 0.95) for extreme intakes of oranges, a HR of 0.86 (95% CI: 0.81, 0.92) for extreme intakes of orange juice, a HR of 0.89 (95% CI: 0.82, 0.99) for extreme intakes of apples and pears, a HR of 0.88 (95% CI: 0.83, 0.93) for extreme intakes of romaine or leaf lettuce, and a HR of 0.93 (95% CI: 0.86, 0.99) comparing those who ate 2 or more servings of walnuts per day versus <1 serving per month.

Table 1.3. Hazard ratios (HR) of incident physical impairment (measured by the Physical Function scale of the SF-36) by top food contributors to AHEI-2010 food components

	Servings				
	Never or <1/month	1-3/month	1/week	≥2/week	*P*-trend
Fruits[1]					
Bananas, 1	1.0 (ref)	0.95 (0.90, 1.00)	0.94 (0.89, 0.99)	0.96 (0.91, 1.01)	0.9
Fresh apples or pears, 1	1.0 (ref)	0.92 (0.85, 1.01)	0.90 (0.82, 0.98)	0.89 (0.82, 0.97)	0.005
Raisin or grapes, ½ cup	1.0 (ref)	0.95 (0.90, 1.00)	0.98 (0.92, 1.03)	0.97 (0.91, 1.03)	0.2
Oranges, 1	1.0 (ref)	0.94 (0.90, 0.97)	0.95 (0.91, 0.99)	0.91 (0.88, 0.95)	<0.001
Peaches or plums, 1 fresh or ½ cup canned	1.0 (ref)	0.93 (0.87, 0.99)	0.95 (0.88, 1.00)	0.96 (0.86, 1.02)	0.06
Vegetables[1]					
Tomatoes, 2 slices	1.0 (ref)	1.04 (0.90, 1.19)	1.08 (0.94, 1.23)	1.05 (0.92, 1.20)	0.4
Iceberg or head lettuce, 1 cup	1.0 (ref)	0.88 (0.81, 0.97)	0.88 (0.81, 0.97)	0.87 (0.80, 0.95)	0.2
Onions as a garnish or in salad, 1 slice	1.0 (ref)	0.96 (0.89, 1.05)	0.93 (0.85, 1.01)	0.95 (0.87, 1.02)	0.4
Romaine or leaf lettuce, 1 cup	1.0 (ref)	0.91 (0.86, 0.97)	0.92 (0.86, 0.98)	0.88 (0.83, 0.93)	0.002
Raw carrots, ½ a carrot or 2-4 sticks	1.0 (ref)	0.96 (0.92, 1.00)	0.97 (0.93, 1.02)	0.95 (0.91, 0.99)	0.02
Nuts/Legumes[1,2]					
Peanut butter, 1 Tbs	1.0 (ref)	1.02 (0.98, 1.07)	1.05 (0.99, 1.11)	1.07 (1.02, 1.13)	0.01
Beans or lentils, ½ cup	1.0 (ref)	0.99 (0.95, 1.03)	0.98 (0.93, 1.03)	1.01 (0.95, 1.07)	0.7
Peanuts, 1oz.	1.0 (ref)	0.97 (0.93, 1.01)	0.98 (0.92, 1.05)	0.97 (0.90, 1.04)	0.8
Other nuts, 1oz.	1.0 (ref)	1.05 (1.01, 1.08)	1.06 (0.99, 1.13)	1.05 (0.99, 1.11)	0.2
Walnuts, 1 oz.	1.0 (ref)	1.00 (0.96, 1.03)	0.93 (0.86, 1.00)	0.93 (0.86, 0.99)	0.02
Red/Processed Meats[1]					
Beef or lamb as a main dish, 4-6 oz.	1.0 (ref)	1.01 (0.97, 1.06)	1.02 (0.97, 1.07)	1.01 (0.96, 1.07)	0.9
Beef or lamb as a mixed dish	1.0 (ref)	1.00 (0.96, 1.04)	1.02 (0.97, 1.07)	1.06 (1.01, 1.11)	0.002
Lean hamburger, 1 patty	1.0 (ref)	0.98 (0.94, 1.03)	1.02 (0.97, 1.07)	1.04 (0.99, 1.10)	0.008
Pork as a main dish 4-6 oz.	1.0 (ref)	0.89 (0.84, 0.94)	0.88 (0.83, 0.93)	0.89 (0.82, 0.96)	0.1
Bacon, 2 slices	1.0 (ref)	1.03 (1.01, 1.06)	1.08 (1.05, 1.12)	1.11 (1.06, 1.17)	0.01

Table 1.3 (Continued).

	Servings				
	Never or <1/month	1-3/month	1/week	≥2/week	*P*-trend
Sugar Sweetened Beverages[1]					
Orange juice, small glass	1.0 (ref)	0.90 (0.84, 0.95)	0.88 (0.82, 0.94)	0.86 (0.81, 0.92)	<0.001
Other fruit juice, small glass	1.0 (ref)	1.05 (1.02, 1.08)	1.08 (1.04, 1.12)	1.11 (1.08, 1.15)	<0.001
Punch, lemonade, sports drinks, or sugared ice tea, 1 glass, bottle, or can	1.0 (ref)	0.98 (0.93, 1.03)	0.96 (0.90, 1.02)	1.02 (0.96, 1.08)	0.004
Carbonated beverage with caffeine and sugar, 1 glass, bottle, or can	1.0 (ref)	0.95 (0.93, 0.99)	0.98 (0.93, 1.03)	0.97 (0.93, 1.02)	0.1
Other carbonated beverages with sugar, 1 glass, bottle, or can	1.0 (ref)	0.90 (0.86, 0.94)	0.94 (0.88, 1.01)	0.99 (0.93, 1.06)	0.007

[1] Models adjusted for BMI (continuous), total caloric intake (quintiles), physical activity (<3.0, 3.0-8.9, 9.0-17.9, 18.0-26.9, ≥27 mets/wk), SF-36 mental health index (continuous), smoking (never, past, current 1-14 cigs/day, current 15-24 cigs/day, ≥25 cigs/day), hypertension (yes, no), high cholesterol (yes/no), myocardial infarction (yes/no), stroke (yes/no), type 2 diabetes (yes/no) and the AHEI-2010 score without the component of interest.

[2] Follow-up started in 2000

DISCUSSION

In this large, prospective study, greater adherence to the AHEI-2010 was associated with a lower risk of developing physical impairment over 18 years of follow-up. Overall, the AHEI diet pattern appeared more strongly associated with physical function than the individual components, or individual foods, although greater intake of vegetables, fruits and moderate alcohol, and lower intake of sugar-sweetened beverages, *trans* fat, and sodium were all significantly associated with modestly lower rates of incident physical impairment. Similarly, greater intakes of oranges, orange juice, apples and pears, romaine or leaf lettuce, and walnuts were associated with reduced risk of physical function impairment.

Our results are consistent with the existing, although limited, literature that supports an association between diet quality and physical function. Most prior studies have been cross-sectional with modest sample sizes. These studies have reported that better diet quality is associated with better physical function, as measured by the SF-36 combined with an in-person assessment (19), or self-reported disability (20); in two cross-sectional studies which also utilized the SF-36 PFS as in our analysis, participants with better diet quality had significantly higher mean physical function scores (21, 22). However, in cross-sectional studies, it is plausible that better physical function may lead to better diet rather than the reverse. To our knowledge, there has been only one prospective study conducted. Among 3,000 participants in a French cohort of middle-aged adults, those with best adherence to dietary guidelines had increased physical function scores as measured by the SF-36 over the 12 year follow-up period (23), consistent with our findings. The epidemiologic research is supported by biologic research demonstrating that higher adherence to the AHEI-2010 is associated with a better lipid and

inflammatory profile, and decreased risk of clinical vascular disease (6). These factors are all strongly related to physical function (7-9) and thus provide a clear biological rationale for the findings observed in this analysis.

One somewhat surprising overall finding was that increased intake of nuts and legumes was associated with an increased risk of physical impairment. However, after we separated this component into the top 5 food contributors, we found the association was driven by increased intake of peanut butter, with no increased risk associated with peanuts, or other nuts, and a significantly reduced risk of impairment with greater walnut intake. Thus, there is no clear explanation for this isolated increase with peanut butter, and it could potentially be a chance finding but deserves further investigation. Moreover, recent evidence from the PREDIMED randomized trial has demonstrated that a Mediterranean diet (made up of components very similar to the AHEI-2010 (6)) supplemented with mixed nuts (24), leads to reduced blood pressure (25) and LDL cholesterol levels (26) and a reduction in the incidence of type 2 diabetes (27) and cardiovascular disease (28) compared to placebo; these are all associated with diminished physical function (7-9).

Our study has numerous strengths including the prospective design with 18 years of follow-up, multiple measures of diet and physical function, the ability to control for multiple potential confounders, and large sample size. Potential limitations also need to be considered. Residual confounding cannot be ruled out in an observational study and thus results should be interpreted with caution. However, associations between diet quality and physical function remained strong and significant after adjustment for a wide array of health and lifestyle factors. Secondly, there is

potential for measurement error in both the dietary assessment and the outcome measurement. However, both assessment instruments are validated and cumulative averages of diet were used to reduce measurement error of the exposure. Additionally, dietary intake was collected prospectively and thus any misreporting of diet is expected to be random and would result in bias to the null, suggesting that our results may underestimate true associations.

In summary, we found that better diet quality as measured by the AHEI-2010 was associated with a lower risk of incident physical impairment among older women, and that the overall diet quality appeared more important than individual components or foods. Given the value of physical function to healthy aging and quality of life, this may represent a particularly compelling public health rationale for persons to improve their diet.

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SEX RELATED DIFFERENCES IN PHYSICAL FUNCTION AND PHYSICAL FUNCTION DECLINE

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ABSTRACT

Background: Physical function is a key component of healthy aging and is central to quality of life in older adults. Numerous studies have consistently demonstrated that women have worse physical function with aging compared to men, however, the explanation for this sex difference is not fully understood.

Methods: We utilized data from Nurses' Health Study and Health Professionals Follow-Up Study, two large cohorts of male and female health professionals, with multiple measures of physical function, measured by the Medical Outcomes Short Form-36 (SF-36) physical function scale (PFS), to examine the role of sex and trajectories of physical function decline. We used multivariable adjusted linear mixed models to estimate the differences in baseline physical function and slopes of physical function decline between men and women. We also investigated the associations between plasma sex hormone levels, a primary biological factor which could be part of the sex difference, and rate of physical function decline in each cohort.

Results: We found that women have both worse baseline physical function scores at mid-life and older ages (age-standardized PFS in men: 86.5 points (95% CI: 86.3, 86.7) vs. PFS in women 80.4 (95% CI: 80.3, 80.6)), and steeper rates of decline in physical function with aging compared to men (age-standardized decline in PFS per year in men: 0.70 points (95% CI: -0.73, -0.68), age-standardized decline in PFS per year in women: 1.34 points (95% CI: -1.36, -1.22), (p-value for sex-difference <0.001)). In particular, in the youngest age group, those less than 55 years of age, risk factor differences – especially body mass index – appeared to account for approximately one-quarter of the sex differences in subsequent decline in function. In both cohorts, we found no suggestion of a relationship between a variety of plasma hormone levels and rate of physical function decline.

Conclusions: In this large cohort of middle-aged and older men and women, we found that women have consistently worse physical function and steeper rates of decline over time compared to men. Given the value of physical function to healthy aging and quality of life, these findings suggest a particularly compelling public health rationale for women to improve their risk factor profiles to prevent physical function impairments with aging.

INTRODUCTION

Physical function is a key component of healthy aging and is central to quality of life in older adults. Prior research has demonstrated that poor physical function is related to hospitalization (1), long-term nursing home care (2, 3), and increase mortality (3, 4) among older adults. With the proportion of the population 65 years or older expected to increase to nearly 20% by the year 2030, identifying factors to prevent or delay physical function decline with aging is of great importance (5).

Numerous studies have consistently demonstrated that women have worse physical function with aging compared to men (6-8). However, the explanation for this sex difference is not fully understood. One hypothesis suggests that differences may simply be due to women's greater likelihood to report physical symptoms compared to men (9, 10). However, there is evidence from some cross-sectional studies that observed sex differences in physical function may be due to risk factor differences, especially varying prevalences of chronic health conditions or lifestyle factors (8, 11, 12), yet the cross-sectional studies are somewhat difficult to interpret, since the study design does not permit differentiation of cause and effect, and it is possible that health and lifestyle may change as a result of physical function rather than explain the onset of impairments in function.

To our knowledge, there have been limited prospective studies on the association of sex differences in relation to physical function decline. Thus, we utilized data from Nurses' Health Study and Health Professionals Follow-Up Study, two large cohorts of male and female health professionals, with multiple measures of physical function to examine this relationship. In addition to examining the role of sex and trajectories of physical function decline, we also

utilized biological and lifestyle data to address the mechanism underlying this possible sex disparity.

METHODS

Study Population

The Nurses' Health Study (NHS) began in 1976, when 121,700 female registered nurses, aged 30-55 years, completed a mailed questionnaire on their health and lifestyle. The Health Professionals Follow-Up Study (HPFS) is a companion study, which began in 1986 when 51,529 U.S. male health professionals (dentists, pharmacists, optometrists, osteopath physicians, podiatrists, and veterinarians) aged 40-75 years, completed a similar questionnaire. Participants have been followed biennially with mailed questionnaires to update information on health and lifestyle. The follow-up rate remains approximately >85-90% in both cohorts. The study was approved by the Institutional Review Boards of Brigham and Women's Hospital (Boston, MA) and the Harvard School of Public Health (Boston, MA).

Physical Function Assessment

Information on physical function was collected using the Medical Outcomes Short Form (SF)-36 questionnaire, a widely used and validated instrument (13). The PFS was administered to participants in both cohorts on the mailed questionnaires starting in 1996, and is comprised of 10 questions regarding physical limitations in performing the following activities: bathing/dressing, walking one block, walking several blocks, walking more than one mile, bending/kneeling, climbing stairs, lifting groceries, moderate activities, and vigorous activities. Each question has the same three possible responses. Each answer of 'Yes, limited a lot' is assigned one point, 'Yes, limited a little' is assigned two points, and an answer of 'No, not limited at all' is assigned three points. A raw score is calculated from the set of 10 questions and ranges from a minimum

of 10 points to a maximum of 30 points. The raw score is then transformed to a 100-point scale, with a score of 100 considered highest physical function (14).

Measurement of Risk Factors

Demographic variables included age (continuous in months). Body mass index (BMI, kg/m^2) was calculated from self-reported height and weight. Lifestyle factors included smoking status (current, former, never), alcohol consumption (non-drinker, 1-14 g/day, ≥15 g/day), physical activity (metabolic equivalent tasks [METs] per week), which was measured using a validated physical activity questionnaire, and the Alternative Healthy Eating Index-2010 (AHEI-2010) (15), a measure of diet quality. Comorbidities included a history of self-reported type 2 diabetes, hypertension, high cholesterol, myocardial infarction, or stroke, which were reported on each biennial questionnaire. All these variables were updated at each two-year questionnaire cycle, except for AHEI-2010 which was updated every four years. We did not update physical activity since levels of physical activity, more so than other variables, may reflect current physical function, and thus earlier-life physical activity may be a better marker of confounding than later activity.

Biomarker Assessment

Blood samples were collected from 32,826 women in the NHS from 1989 to 1990 and from 18,225 men in HPFS from 1993 to 1995. Details on blood draw, transportation, and storage of plasma samples have been previous described (16, 17). Briefly, willing participants were sent a venipuncture kit, had their blood drawn, and returned the samples to us by overnight mail, on ice. Upon receipt by our lab, an average 24 hours after blood draw, samples were processed,

aliquotted and stored in liquid nitrogen freezers. In this analysis, measures of sex hormones were utilized from previous research in the NHS and HPFS, including nested case-control studies of breast cancer, ovarian cancer, colon cancer, prostate cancer, rheumatoid arthritis, inflammatory bowel disease, stroke, and myocardial infarction.

Measured sex hormones in NHS included bound levels of plasma estrone, estrone sulfate, estradiol, androstenedione, testosterone, dehydroepiandrosterone (DHEA), and dehydroepiandrosterone sulfate (DHEA-S). In HPFS, bound levels of plasma estrone, estradiol, and testosterone were measured. All hormones except DHEA and DHEA-S were measured by radioimmunoassay at the Quest Diagnostics Nichols Institute (San Juan Capistrano, CA) or by liquid chromatography-tandem mass spectrometry (ThermoFisher Scientific, Franklin, MA and Applied Biosystems-MDS Sciex, Foster City, CA) at the Mayo Medical Laboratories (Rochester, MN). DHEA was measured by radioimmunoassay (Diagnostic Systems Laboratories, Webster, TX) at Quest Diagnostics or by the quantitative sandwich enzyme immunoassay technique at Dr. Nader Rifai's laboratory at the Department of Laboratory Medicine, Children's Hospital Boston (Boston, MA). DHEA-S was measured by the Immulite 2000 a solid-phase, chemiluminescent immunoassay (Siemens Medial Solutions, Los Angeles, CA) at Quest Diagnostics and Mayo Medical Laboratories, or by a coated-tube radioimmunoassay at Dr. Rifai's laboratory. Average overall coefficients of variation from the measured batches were within acceptable ranges. We adjusted for inter-batch variation using the average-batch calibration method, described by Rosner et al (18).

Statistical Analysis

The main analysis of sex differences in physical function included 80,866 women from NHS and 35,094 men from HPFS. In order to be included in this analysis, participants had to provide information on physical function at baseline in 1996. Thus, analyses of baseline physical function included all these participants. In analyses of trajectories of function, there were 5,885 participants in NHS and 3,123 participants in HPFS who were excluded since they did not have any measures of physical function after baseline (an additional 13,372 women and 8,263 men were excluded after baseline due to death). Women who were lost to follow-up and did not have PFS after baseline were highly similar to those who provided data after baseline; for example, they were only slightly older (64.2 vs. 62.6 years, respectively), BMI was virtually identical (26.2 kg/m^2 vs. 26.1 kg/m^2), AHEI-2010 score (53.7 vs. 53.3) was nearly identical, and prevalence of former smokers (42.0% vs. 43.6%) was also very similar. Baseline PFS scores in women who did not have follow-up measures were less than 5% lower (76.9 vs. 80.3). In men, there were also few meaningful differences between those who were lost to follow-up and those who contributed to analyses of change in physical function. Thus, we do not expect any meaningful bias due to missing physical function data over time.

To calculate age-adjusted baseline physical function and age-adjusted average rate of change in physical function per year, we fit linear mixed effect models separately in each cohort; we also fit separate models within age strata in each cohort. Models included random varying intercepts and slopes to allow for individual physical function trajectories over time. To evaluate the association between gender and trajectories of physical function decline, we used multivariable-adjusted, linear mixed effects models to estimate mean differences in rates of physical function

decline over the follow-up period. A series of models were fit, each accounting for additional potential risk factor groupings for physical function decline.

Multivariable-adjusted, linear mixed models were also used to test the association between plasma hormone levels and trajectories of physical function decline. Tests of trend were conducted by modeling the median value of each category of hormone level as a continuous variable. All analyses were performed in SAS 9.3 (SAS Institute Inc., Cary, NC).

RESULTS

Characteristics of the Study Population

Characteristics of study participants in each cohort at baseline in 1996 are presented in Table 2.1. Overall, men and women were similar in mean age, BMI, and AHEI-2010 diet score. Men tended to exercise more, smoke cigarettes less, and were more likely to be moderate drinkers compared to women. A greater percentage of women had hypertension and high cholesterol while a greater percentage of men had a history of myocardial infarction.

Table 2.1. Baseline characteristics of NHS and HPFS participants in 1996

	Women (NHS) (n=80,866)	**Men (HPFS)** (n=32,094)
Age, yrs	62.6 (7.1)	63.5 (9.3)
Body mass index, kg/m^2	26.6 (5.3)	25.9 (3.5)
Physical activity, MET-hr/week	17.8 (22.0)	29.5 (29.3)
Smoking, %		
Never	45.8	43.3
Former	43.6	51.2
Current	10.6	5.5
Alcohol intake, %		
0 g/d	40.1	23.9
1-14 g/d	50.9	50.2
≥ 15 g/d	9.0	25.9
AHEI-2010	53.3 (10.4)	54.3 (11.2)
Diabetes, %	6.9	6.2
Hypertension, %	41.1	34.4
High cholesterol, %	54.6	45.2
Myocardial infarction, %	1.0	7.9
Baseline physical function score	80.3 (21.9)	86.7 (19.4)

Values are means(SD) or percentages

Gender Differences in Baseline Physical Function and in Physical Function Decline over Time

Overall, after adjusting for age, men had higher physical function scores at baseline compared to women (age-standardized PFS score in men: 86.5 points (95% CI: 86.3, 86.7) vs. PFS score in women 80.4 (95% CI: 80.3, 80.6)). To examine if these differences may vary by age groups, we calculated PFS scores in several age strata. As expected in both men and women, mean PFS score decreased with increasing age categories (Table 2.2). However, men consistently had higher physical function scores compared to women within each age strata. For example, the age-adjusted PFS score in women ≤55 years was 87.2 (95% CI: 86.9, 87.5) and the PFS Score in women >65 years was 74.3 (95% CI: 74.0, 74.5); in contrast, the PFS score in men ≤55 years was 93.4 (95% CI: 93.1, 93.7, p-value for sex-difference <0.001) and the PFS score in men >65 year was 79.9 (95% CI: 79.6, 80.3, p-value for sex-difference <0.001). (Table 2.2)

Table 2.2. Age-adjusted mixed model results for baseline physical function and average rate of change overall, and stratified by age*

	Women (NHS)	Men (HPFS)	P-value for difference
Overall	**(n=80,866)**	**(n=35,094)**	
Baseline SF-36 Physical Function Score	80.4 (80.3, 80.6)	86.5 (86.3, 86.7)	<0.001
Avg Rate of Change per year	-1.34 (-1.36, -1.33)	-0.70 (-0.73, -0.68)	<0.001
≤ 55 years of age	**(n=15,271)**	**(n=8,892)**	
Baseline SF-36 Physical Function Score	87.2 (86.9, 87.5)	93.4 (93.1, 93.7)	<0.001
Avg Rate of Change per year	-0.66 (-0.69, -0.64)	-0.46 (-0.50, -0.43)	<0.001
55-65 years of age	**(n=33,831)**	**(n=11,040)**	
Baseline SF-36 Physical Function Score	83.3 (83.1, 83.5)	90.0 (89.7, 90.3)	<0.001
Avg Rate of Change per year	-1.10 (-1.11, -1.08)	-0.71 (-0.74, -0.67)	<0.001
> 65 years of age	**(n=31,764)**	**(n=15,162)**	
Baseline SF-36 Physical Function Score	74.3 (74.0, 74.5)	79.9 (79.6, 80.3)	<0.001
Avg Rate of Change per year	-1.94 (-1.97, -1.92)	-1.38 (-1.42, -1.33)	<0.001

*Physical function determined by score on Medical Outcomes Short Form-36 Physical Function Scale, scores can range from 0-100, with higher scores indicating better function.

Similarly, when we examined change in physical function over time, both men and women had significant declines in physical function score over time; however, the average rate of decline per year was significantly greater in women compared to men. After adjusting for age, we found an average decline of 1.34 points (95% CI: -1.36, -1.22) in physical function score per year in women, while men on average declined 0.70 points (95% CI: -0.73, -0.68) per year (p-value for sex-difference <0.001). When we stratified by age, in both men and women, the average rate of decline increased with increasing age category (Table 2.2), however, within each age category, women still declined at a significantly faster rate compared to men (all p-values<0.001). (Table 2.2)

Physical Function Risk Factors Differences in Men and Women

To evaluate to what extent the observed sex differences in physical function and rate of decline could be explained by differences in risk factors in men and women, we created a series of models, including various groups of physical function risk factors. In the first model, including only age as a covariate, the mean difference in baseline physical function for women versus men was -5.16 points (95% CI: -5.42, -4.90) and the mean difference in the rate of decline in physical function score per year was -0.43 points (95% CI: -0.46, -0.41). When we added BMI to the model, the mean baseline difference was attenuated by 13%, indicating differences in BMI between the sexes partially explained the observed differences in physical function (mean baseline difference in women vs. men: -4.51 (95% CI: -4.77, -4.26)). In subsequent models adding health behaviors (smoking status, alcohol consumption, AHEI-2010 score) and comorbidities (hypertension, high cholesterol, myocardial infarction, type II diabetes), both estimates were further attenuated, although to a lesser extent. In a model including all these risk factors for physical function decline and baseline physical activity, we found that these risk factors taken together explained over 45% of the observed sex difference in baseline physical function score and 12% of the observed difference in mean rate of decline (mean baseline difference in women vs men: -2.74 (95% CI: -3.00,-2.47), mean difference in annual rate of change for women vs. men: -0.38 (95% CI: -0.41, -0.36)). We also looked at a model with all risk factors except for physical activity since we were concerned about the interpretation of physical activity in models for physical function and the possibility of reverse causation. In this model, the baseline difference comparing women vs. men was -4.10 (95% CI: -4.36, -3.83) and the mean difference in annual rate of change was nearly identical to the estimate from the model

including physical activity (mean difference for women vs. men: -0.38 (95% CI: -0.41, -0.36)).

(Table 2.3)

Table 2.3. Mean difference baseline physical function difference and annual rate of change in physical function, in women versus men*

	Mean baseline difference for women vs. men	Mean difference in annual rate of change for women vs. men
Overall		
Model 1	-5.16 (-5.42, -4.90)	-0.43 (-0.46, -0.41)
Model 2	-4.51 (-4.77, -4.26)	-0.45 (-0.48, -0.43)
Model 3	-3.96 (-4.21, -3.70)	-0.40 (-0.43, -0.38)
Model 4	-4.10 (-4.36, -3.83)	-0.39 (-0.42, -0.37)
Model 5	-2.74 (-3.00, -2.47)	-0.38 (-0.41, -0.36)
≤ 55 years of age at baseline		
Model 1	-5.02 (-5.58, -4.45)	-0.29 (-0.34, -0.24)
Model 2	-4.64 (-5.19, -4.08)	-0.24 (-0.29, -0.19)
Model 3	-4.33 (-4.89, -3.77)	-0.22 (-0.27, -0.17)
Model 4	-4.26 (-4.82, -3.70)	-0.22 (-0.27, -0.17)
Model 5	-3.66 (-4.23, -3.09)	-0.22 (-0.27, -0.17)
55-65 years of age at baseline		
Model 1	-5.48 (-5.92, -5.04)	-0.44 (-0.48, -0.40)
Model 2	-4.95 (-5.39, -4.52)	-0.45 (-0.50, -0.41)
Model 3	-4.34 (-4.78, -3.90)	-0.41 (-0.45, -0.37)
Model 4	-4.37 (-4.81, -3.93)	-0.40 (-0.44, -0.36)
Model 5	-3.27 (-3.71, -2.82)	-0.39 (-0.43, -0.35)
> 65 years of age at baseline		
Model 1	-6.40 (-6.84, -5.95)	-0.61 (-0.66, -0.56)
Model 2	-5.78 (-6.23, -5.34)	-0.68 (-0.73, -0.62)
Model 3	-5.69 (-6.13, -5.25)	-0.65 (-0.70, -0.60)
Model 4	-5.49 (-5.95, -5.03)	-0.58 (-0.63, -0.52)
Model 5	-3.37 (-3.83, -2.91)	-0.55 (-0.61, -0.50)

*Physical function determined by score on Medical Outcomes Short Form-36 Physical Function Scale, scores can range from 0-100, with higher scores indicating better function.
Model 1 adjusts for age (continuous).
Model 2 adjusts for age (continuous), BMI (continuous).
Model 3 adjusts for age (continuous), BMI (continuous), smoking status (never, past, current), alcohol consumption (0 g/d, 1-14g/d, 15+ g/d), AHEI-2010 (continuous)
Model 4 adjusts for age (continuous), BMI (continuous), smoking status (never, past, current), alcohol consumption (0 g/d, 1-14g/d, 15+ g/d), AHEI-2010 (continuous) hypertension (yes/no), high cholesterol (yes/no), myocardial infarction (yes/no), type 2 diabetes (yes/no).
Model 5 adjusts for age (continuous), BMI (continuous), smoking status (never, past, current), alcohol consumption (0 g/d, 1-14g/d, 15+ g/d), AHEI-2010 (continuous) hypertension (yes/no), high cholesterol (yes/no), myocardial infarction (yes/no), type 2 diabetes (yes/no), physical activity (continuous)

We also examined these models after stratifying by age. Overall, we found that risk factors explained more of the observed sex differences for physical function decline among younger participants compared to older participants. (Table 2.3) Among those 55 years of age or less at baseline, risk factors explained 24% of the observed difference in mean rate of decline (mean difference in annual rate of change for women vs. men: -0.22 (95% CI: -0.27, -0.17)). While among those over 65 years of age at baseline, risk factors explained 5% of the observed difference in mean rate of decline (mean difference in annual rate of change for women vs. men: -0.58 (95% CI: -0.63, -0.52)).

Sex Hormones and Physical Function

We also examined sex hormones as primary biological factors which could be part of sex differences in physical function. We investigated the associations between plasma sex hormone levels and rate of physical function decline in each cohort. In both cohorts, we found no suggestion of a relationship between a variety of plasma hormone levels and rate of physical function decline. For example, among women, comparing those in the highest to lowest quartile of plasma estradiol, we found no difference in mean rate of physical function decline, after multivariable adjustment (mean difference -0.01 (95% CI: -0.19, 0.16, p-trend=0.8). Results were similar for estrone and also for testosterone levels in women (Q4 vs Q1: estrone: -0.01, 95% CI: -0.18, 0.16, p-trend=0.9, testosterone: -0.08, 95% CI: -0.19, 0.03, p-trend=0.1) (Table 2.4). Similarly, among men, comparing those in highest to lowest tertile of plasma hormone levels (due to the smaller sample of men with relevant data, we created tertiles rather quartiles), we found null results for mean differences in rates of physical function decline (T3 vs T1:

estradiol: -0.11, 95% CI: -0.49, 0.29, p-trend=0.6, estrone: -0.26, 95% CI: -0.78, 0.29, p-trend=0.4, testosterone: -0.08, 95% CI: -0.44, 0.26, p-trend=0.7) (Table 2.5).

Table 2.4. Mean differences in slopes of physical function decline in the Nurses' Health Study by quartiles of plasma hormone levels

	Q1 (reference)	Q2	Q3	Q4	p-trend
Estradiol (n=2,682)					
Median	3.52 pg/mL	5.10 pg/mL	7.37 pg/mL	12.51 pg/mL	
Model 1	0.00	-0.15 (-0.30, 0.01)	-0.13 (-0.29, 0.02)	-0.25 (-0.41, -0.10)	0.004
Model 2	0.00	-0.10 (-0.25, 0.06)	-0.03 (-0.18, 0.13)	-0.01 (-0.19, 0.16)	0.8
Estrone (n=2,559)					
Median	15.34 pg/mL	22.40 pg/mL	30.05 pg/mL	44.73 pg/mL	
Model 1	0.00	-0.03 (-0.19, 0.13)	-0.09 (-0.25, 0.07)	-0.18 (-0.34, -0.02)	0.02
Model 2	0.00	-0.03 (-0.19, 0.13)	-0.03 (-0.20, 0.13)	-0.01 (-0.18, 0.16)	0.9
Testosterone (n=5,326)					
Median	10.87 ng/dL	16.85 ng/dL	23.27 ng/dL	34.90 ng/dL	
Model 1	0.00	-0.02 (-0.13, 0.09)	-0.07 (-0.18, 0.04)	-0.10 (-0.21, 0.01)	0.06
Model 2	0.00	-0.03 (-0.14, 0.08)	-0.06 (-0.17, 0.05)	-0.08 (-0.19, 0.03)	0.1

Model 1 adjusts for age (continuous)

Model 2 adjusts for age (continuous), BMI (continuous), smoking status (never, past, current), alcohol consumption (0 g/d, 1-14g/d, 15+ g/d), AHEI-2010 (continuous) hypertension (yes/no), high cholesterol (yes/no), myocardial infarction (yes/no), type 2 diabetes (yes/no), physical activity (continuous)

Table 2.5. Mean differences in slopes of physical function decline in the Health Professionals Follow-Up Study by tertiles of plasma hormone levels

	T1 (reference)	T2	T3	p-trend
Estradiol (n=1,165)				
Median	18.83 pg/mL	25.11 pg/mL	32.11 pg/mL	
Model 1	0.00	0.11 (-0.15, 0.37)	-0.03 (-0.29, 0.24)	0.8
Model 2	0.00	0.14 (-0.23, 0.51)	-0.11 (-0.49, 0.28)	0.6
Estrone (n=611)				
Median	20.75 pg/mL	29.16 pg/mL	39.96 pg/mL	
Model 1	0.00	-0.02 (-0.39, 0.34)	-0.21 (-0.58, 0.17)	0.3
Model 2	0.00	0.03 (-0.47, 0.54)	-0.25 (-0.78, 0.29)	0.4
Testosterone (n=1,387)				
Median	10.87 ng/mL	16.85 ng/mL	23.27 ng/mL	
Model 1	0.00	-0.08 (-0.32, 0.16)	0.01 (-0.24, 0.25)	0.9
Model 2	0.00	-0.13 (-0.49, 0.22)	-0.09 (-0.44, 0.26)	0.7

Model 1 adjusts for age (continuous)

Model 2 adjusts for age (continuous), BMI (continuous), smoking status (never, past, current), alcohol consumption (0 g/d, 1-14g/d, 15+ g/d), AHEI-2010 (continuous) hypertension (yes/no), high cholesterol (yes/no), myocardial infarction (yes/no), type 2 diabetes (yes/no), physical activity (continuous)

DISCUSSION

In this large, prospective study of women and men, we found gender differences in physical function at baseline and in trajectories of physical function decline over time. Even across age strata, women had consistently worse baseline physical function and steeper rates of decline compared to men. In particular, we found that risk factors appeared to explain 24% of the differences in physical function decline in the youngest age group (≤55 years), indicating that it could be of particular importance to intervene on risk factors in women to prevent further physical function impairments with aging.

These findings are consistent with prior literature regarding gender differences and physical function (6-8, 10, 19, 20). For example, among a cohort of 10,263 U.S community dwelling adults followed for up to 7 years, women were more likely to report impairments in mobility (inability to climb stairs or inability to walk half a mile without assistance) and were more likely to continue to report impairments in mobility over the follow-up period compared to men (relative risk comparing men vs. women for recovering from an impairment: 0.72 (95% CI: 0.53, 0.98)) (7). Other studies have also reported similar findings; however, most have been cross-sectional and could not evaluate whether differences were only at a single time point or persisted over time (6, 10).

Overall, we found that differences in the risk factor profiles of women and men explained 20% of the sex differences in baseline physical function and 9% of the sex differences in annual rate of change. Most importantly however, among the youngest age group (≤55 years of age at baseline), risk factors differences explained 24% of the difference in annual rate of change for women compared to men, suggesting that risk factor modification could be especially beneficial

in younger women to prevent further losses in physical function with aging. Moreover, we observed that BMI accounted for the greatest attenuation in the mean difference in change for women vs. men compared with the other risk factors in the ≤55 age group. These findings are consistent with prior studies that have investigated differences in body composition and BMI as possible explanations for sex differences in physical function. In the Health, Aging and Body Composition study, higher fat mass explained 35% of the poorer physical function observed among women compared to men (21). Taken together with the findings in this analysis, research suggests that women should be particularly encouraged to achieve and maintain a healthy weight at middle age to prevent impairments in physical function and physical function decline.

A strength of this analysis was our ability to investigate numerous potential risk factors and evaluate their impact in explaining sex differences in physical function and physical function decline. However, there could be other potential, unknown risk factors that could be important in explaining the observed sex differences. One hypothesis that has been put forth for these gender differences is that women are more likely to report symptoms of physical impairment compared to men (8, 9). It is possible that our participants, as health professionals, are more accurate at reporting health symptoms such as physical function, although we have no means of assessing their tendency to report such symptoms here.

Sex differences in physical function could also be due to biological differences between men and women. In this analysis, we also explored how plasma sex hormones were related to physical function decline in women and men, as a way to examine a primary biological difference between the sexes. However, we found no evidence of a relationship between plasma estrogens or testosterone levels and subsequent trajectories of physical function decline in men or women.

To our knowledge, there has been one other study that has studied this relationship. In a cross-sectional analysis of 1,200 older adults, there were no associations in men or women found between total estradiol levels or total testosterone levels with physical performance or physical limitations. However, it was found that men in the highest quartile of estradiol/SHBG ratio had significantly greater physical performance compared to men in the lowest quartile and bioavailable testosterone was positively associated with physical performance in men (22). Nonetheless, there certainly is not convincing evidence that sex hormones may play a role in physical function, and it remains unclear whether biologic differences between women and men may help to explain observed sex differences in physical function.

Our study has numerous strengths including the prospective design with over 10 years of follow-up, multiple measures of physical function over time, the ability to investigate multiple potential risk factors and biological data, and a large sample size. Potential limitations also need to be considered. There is potential for measurement error in both the assessment of risk factors and the outcome measurement. We would expect any misreporting of risk factors to be random and thus results would be biased toward the null, suggesting there could be further attenuation of the estimates for gender differences in relation to physical function decline with more accurate measurements of risk factors; thus, we could be somewhat underestimating the extent to which risk factor differences explain sex differences. Finally, our study population was homogenous, comprised of predominately white health professionals, thus it is possible our findings may not be generalizable to other racial or ethnic groups. However, the homogeneity and the uniform health education of this population should provide strong internal validity of our findings.

In summary, we found that women have both worse baseline physical function scores at mid-life and older ages, and steeper rates of decline in physical function with aging, compared to men. In particular, in the youngest age group we examined, those less than 55 years of age, risk factor differences – especially body mass index – appeared to account for approximately one-quarter of the sex differences in subsequent decline in function. Our findings suggest that middle-aged women may be targeted for risk factors modification, including weight counseling. Given the value of physical function to healthy aging and quality of life for most people, this may represent a particularly compelling public health rationale for women to improve their risk factor profiles to prevent physical function impairments with aging.

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